

could be helpful in evaluating the results of compression in individual patients. This method could also be useful for trials in which bandaging systems are compared.

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## Atypical Autoimmune Blistering Dermatitis Associated with Sjögren's Syndrome

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Accepted June 12, 2002.

Sir,

Sjögren's syndrome (SS) is a chronic autoimmune rheumatic disease characterized by dryness of the eyes and mouth resulting from lymphocytic infiltration of the lacrimal and salivary glands. In primary SS, these obligatory symptoms may be alone or accompanied by systemic manifestations (articular, renal, vascular, etc.), but no other well-defined connective tissue disease can be diagnosed on the basis of these systemic symptoms. In secondary SS, other rheumatic diseases, commonly rheumatoid arthritis or systemic lupus erythematoses (SLE), are coupled with the obligatory sicca symptoms (1, 2).

Immunopathologically, circulating autoantibodies, autoimmune inflammation, lymphocytic infiltration, and the consequent destruction of the affected tissues are the main features of the syndrome. Whereas bullous skin symptoms are commonly associated with generalized autoimmune diseases such as SLE (3, 4), we report here on a patient with primary SS in whom a blistering skin eruption developed, along with the presence of autoantibodies against type VII collagen.

## CASE REPORT

A 56-year-old woman was admitted to the Department of Dermatology because of itchy, partly blistering skin eruptions in 1998. Her medical history included hypertension,

thyroidectomy, subjective xerophthalmia and xerostomia, and since 1994 she had been followed for primary SS. At that time, ophthalmological examination indicated significantly reduced lacrimation (Schirmer's test: 1 mm/5 min) on both eyes. Because of the severe eye dryness, artificial stopping of the lacrimal ducts was performed. Salivary gland scintigraphy, together with the unstimulated and stimulated saliva production, revealed markedly decreased salivary function. The parotid gland sonography demonstrated a gross parenchymal inhomogeneity characteristic of primary SS (5). The abnormal laboratory findings included mild hypergammaglobulinaemia (21.1 g/l, normal value 7.5–18 g/l), IgM rheumatoid factor positivity (73.6 U/ml; normal value <14 U/ml), anti-SSA/Ro antibody positivity, and an elevated serum  $\beta_2$ -microglobulin level (13  $\mu\text{g/ml}$ ; normal value <2  $\mu\text{g/ml}$ ). Anti-dsDNA and anti-SSB/La autoantibodies were not detected. The diagnosis of primary SS was established in accordance with the European Economical Community Criteria (6, 7).

In 1998, she presented with itchy, partly blistering skin eruptions that had lasted for several weeks and showed no tendency to heal in response to local corticosteroid and antiseptic preparations. Because of her previously diagnosed diseases, she was regularly taking levothyroxine, nifedipine, chloroquine and bromhexine-hydrochloride, and she was using artificial tear.

On admission, physical examination revealed numerous 1–2 cm round or oval, reddish papules with or without tense blisters and excoriated erosions on her neck and upper trunk (Fig. 1). No exanthems or erosions were found on the mucous membranes, but a marked dryness was noted. The patient was otherwise in good general health. The clinical symptoms led



Fig. 1. Tense, clear fluid-filled bullae and crust-covered erosions on an erythematous background on the neck and trunk.

to a presumptive diagnosis of bullous pemphigoid (BP), and the patient was hospitalized. Her laboratory findings included an increased erythrocyte sedimentation rate (40 mm/h), leukopenia ( $2.43 \times 10^9/l$ ), neutropenia ( $1.67 \times 10^9/l$ ), lymphopenia ( $0.46 \times 10^9/l$ ), a positive homogeneous pattern of antinuclear antibody on Hep-2 cells, a mildly positive LE-cell phenomenon, high titres of anti-SSA/Ro ( $196 \mu/ml$ ; negative value  $<15 \mu/ml$ , COGENT Diagnostics Ltd.) and a moderately elevated level of anti-dsDNA antibodies (52 IU/ml; negative value  $<40$  IU/ml, COGENT Diagnostics Ltd.). Cryoglobulins, anti-RNP and anti-Sm antibodies were not detected, and the liver and renal function tests and serum protein electrophoresis findings (including the complement C3 level) were in the normal ranges.

Routine histology of the lesional skin revealed subepidermal, non-acantholytic bullae with extensive oedema formation in the papillary dermis and polymorphic perivascular infiltration (Fig. 2a). Direct immunofluorescence examination of the perilesional skin demonstrated linear IgG and C3 binding to the dermal-epidermal junction (Fig. 2b). Indirect immunofluorescence testing on 1 M NaCl-separated normal human skin revealed that the IgG from the patient's serum labelled exclusively the dermal floor of the blisters (Fig. 2c). Circulating autoantibodies against specific antigenic epitopes of the BP autoantigens (BP230 and BP180) were not detected by immunoblotting and an ELISA technique (8–10) (data not shown). Immunoblotting with human dermal protein extracts as substrates indicated the presence of circulating autoantibodies against intact tissue type VII collagen in the patient's serum. The patient's serum reacted with two dermal components, 250 and 270 kDa, the former corresponding to the band obtained with a monoclonal antibody against collagen VII (SIGMA, St. Louis, MO).

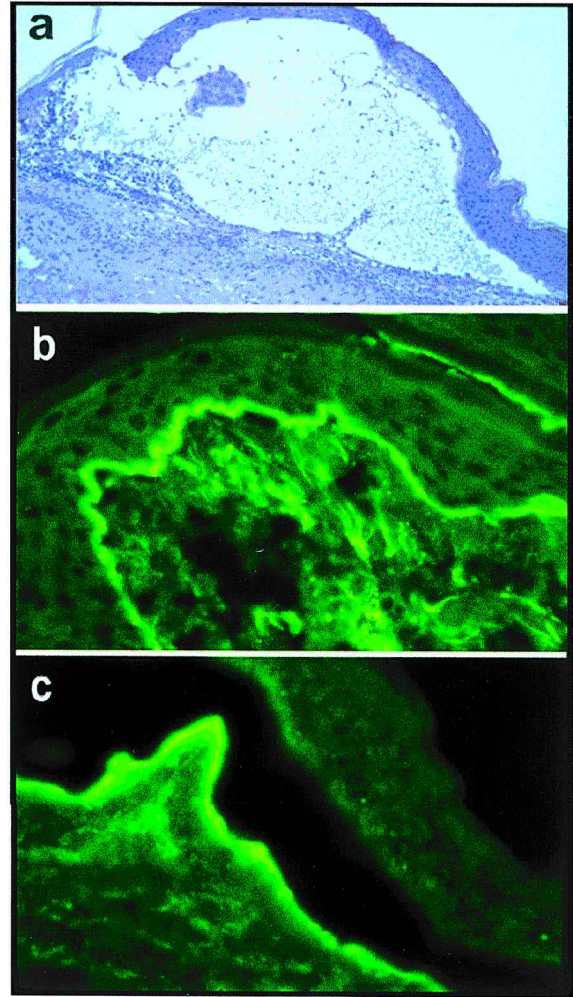


Fig. 2. (a) Histopathologic examination of the subepidermal, non-acantholytic bulla. Note the polymorphic perivascular infiltration and oedema formation in the dermis (haematoxylin-eosin stain; original magnification  $\times 100$ ). (b) Direct immunofluorescence of a perilesional biopsy specimen showing linear deposits of IgG in the basal membrane zone. (c) Indirect immunofluorescence on salt-split normal human skin. IgG autoantibodies from the patient's serum labelled exclusively the dermal floor of the blisters. (Original magnification: b, c,  $\times 160$ )

Medium-dose oral prednisolone (50 mg/day) was started with local antiseptic therapy, and a rapid improvement was observed. The dose of prednisolone was gradually tapered off to 25 mg every other day, and the patient remained symptom-free for 6 months, when she died following an acute myocardial infarction.

## DISCUSSION

We describe a patient with primary SS in whom a blistering skin disease developed. Although her subjective xerophthalmia had been present since 1985, and xerostomia since 1990, the diagnosis of SS was established only in 1994. Besides eyedrops, the patient was treated with chloroquine and bromhexine-hydrochloride, and remained in a good general condition until 1998, when her bullous skin eruption developed.

It was then necessary to exclude BP and other

primary subepidermal bullous diseases with autoantibodies to hemidesmosomal or lamina lucida antigens. The deposition of IgG on the dermal side of the basal membrane zone, together with the presence of circulating autoantibodies to type VII collagen, suggested epidermolysis bullosa acquisita (EBA) and bullous SLE. The absence of mechanical skin fragility and formation of scars and milia exclude the possibility of the mechanobullous (non-inflammatory) form of EBA, but do not exclude the possibility of the generalized inflammatory EBA (11).

As the LE cell phenomenon was mildly positive and the level of the anti-dsDNA antibodies was moderately elevated, the possibility of SLE arose. However, the patient's clinical symptoms and laboratory findings did not meet the SLE criteria of the American Rheumatism Association (12). Apart from this, the case fully satisfied all the immunohistological requirements for bullous SLE (3, 4, 13). 1) An acquired, widespread, non-scarring vesiculobullous eruption; 2) subepidermal blister formation with acute inflammation in the upper dermis; 3) linear IgG and C3 depositions in the dermal-epidermal junction zone; 4) linear IgG deposits on the dermal side of salt-split skin, indicating circulating autoantibodies to components of the lamina densa or anchoring fibrils (such as type VII collagen). The striking similarities between this case and bullous SLE as concerns the clinical, laboratory, immunofluorescence and immunoblotting data led us to believe that this atypical blistering eruption was associated with primary SS. Nevertheless, it cannot be absolutely excluded that in our patient a primary SS was coupled with atypical SLE, forming an overlap syndrome in this patient (13). A long-term follow-up would have solved this diagnostic problem, but this did not prove possible as the patient died following an acute myocardial infarction.

Most SS patients have elevated levels of antibodies against many cellular and nuclear proteins and tissue constituents. The existence of autoantibodies capable of initiating or causing blister formation cannot therefore be excluded in SS. Among others, circulating anti-type VII collagen antibodies were detected in the patient's serum. Since these autoantibodies are presumed to play a central role in blister formation in EBA and bullous SLE (3, 15), we hypothesize that the presence of anti-type VII collagen autoantibodies was directly connected with the blistering skin eruptions in the patient, and these autoantibodies may contribute to the initiation of bullous skin symptoms in other autoimmune disorders as well.

#### ACKNOWLEDGEMENTS

This work was supported by the Hungarian National Committee for Technical Development (OMFB 02211/1999) and OTKA (Grant: T 032 495).

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